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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
WELTER, RACHAEL E	
ART UNIT	PAPER NUMBER
1611	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/886,296	TARARA ET AL.	
	Examiner	Art Unit	
	RACHAEL E. WELTER	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 April 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *57,59-80 and 82-102* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *57, 59-80, 82-102* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/6/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on April 6, 2009 has been entered.

Claim Status

Claims 57, 59-80, 82-102 are pending in this application. Claims 1-56, 58, and 81 stand cancelled.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on April 6, 2009 was in compliance with the provisions of 37 CFR 1.97 and 37 CFR 1.98. Accordingly, the information disclosure statement was considered by the examiner. A signed copy of form 1449 is enclosed herewith.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 57, 59-80, and 82-102 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Independent claims 57, 80, and their dependent claims recite the limitation, "…wherein the particulate microstructures comprise **greater than about** 50% phospholipid." "Greater than" is a maxima and all possible values above 50% are encompassed. "About" indicates a range centered on the recited value. In this case, "about" indicates both values above and below 50%. Therefore, what values are included in the range "greater than about 50% phospholipid" cannot be determined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 57, 59-77, 80, 82-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5,855,913) in view of Unger (6,120,751) as evidenced by 5,776,488. Note US '488 is only relied upon to show the inherent property claimed in claims 72, 80, and 95.

Hanes et al teach aerodynamically light particles for drug delivery to the pulmonary system. The particles have a tap density of less than 0.4 g/cm3, aerodynamic diameter of 3 microns (see column 9, line 45-50), and a mass mean diameter (geometric diameter) between 5 to 30 microns. See abstract, See column 9, lines 26-45, and claim 1. Claim 3 teaches a tap density of less than 0.1 g/cm3. Table 2 teaches the porous microparticles with DPPC (phospholipids) have a density of 0.30 g/cm3. It should be noted that Hanes teaches tap density is a standard measure of the envelope mass density (bulk density) on column 9, lines 5-6. On column 14, lines 36-40, Hanes teaches the bulk density is estimated by tap density measurements.

Hanes teaches the presence of irregular surface structure, or pores or cavities within the particle (this reads on instantly claimed "hollow microstructure") contributes to the aerodynamic lightness. Hanes also teaches the irregular surface texture and porous structure also contributes to the low tap density and manipulation of these features permits the delivery of larger particle envelope volumes into the lungs (col. 9, lines 10-25). Porosity and surface roughness can be increased by varying the inlet and outlet temperatures, among other factors. See column 12, lines 10-13. The aerodynamically light particles may be fabricated to provide a particle sample with a preselected size distribution. For example, greater than 30%, 50%, 70%, or 80% of the particles in a

sample can have a geometric diameter within a selected range of at least 5 microns. The particles contain surfactants such as DPPC (instant gel to liquid temperature; see US 5,776,488 as art of interest) and the microstructures are taught to encapsulate active agents, which allow the active to remain protected (col. 10, lines 37-50 and examples). Note that DPPC is a zwitterionic lipid and is present in an amount of 62.8 wt.% and 89.1 wt.% in Table 4 of Hanes (column 18, lines 35-50). The particles can also be co-delivered with larger carrier particles, not carrying a therapeutic agent, having, for example, a mean diameter ranging between about 50 microns and 100 microns. See column 4, lines 12-15.

Biodegradable polymer, copolymers, or a blend may be utilized. Hanes teaches the use of polyglycolic acid and polylactic acid with a surfactant (DPPC) and the polyester may also have charged or functionizable groups such as amino acids. Other polymers taught are acrylic acids and methacrylic acids and polyvinyl compounds may be used to make the microsphere. See column 5, line 49 to column 6, line 27. Further, the particles may be formed into microspheres by various methods including but not limited to **coacervation (note a coacervate is a spherical aggregation of lipid molecules)**, interfacial polymerization, etc. (note col. 6). Instant therapeutic agents including insulin, growth hormones, etc. are taught on column 10, lines 4-30.

Hanes teaches aerodynamically light PEG particles were prepared by spray drying using 5 g PEG (MW 15,000-20,000, Sigma) and the surfactant such as DPPC may be incorporated into the polymer solution prior to particle formation, or optionally the particles can be ionically or covalently coated by surfactant on the particle surface

after particle formation, or the surfactant may be absorbed onto the particle surface. See column 13, lines 1-25. Note that when DPPC is incorporated into the polymer solution to form the particles, DPPC is part of the structural matrix.

Hanes et al do not teach the use of calcium in the structural matrix.

Unger teaches charged lipids and their use for drug delivery, targeted delivery, etc. See abstract. Unger teaches that prior art studies have described the effects of calcium and other multivalent cations on membrane asymmetry, lipid distribution, vesicle size, aggregation and fusion. The general consensus exists that multivalent cations, such as calcium and magnesium, in the external environment of phospholipid vesicles cause the structures to aggregate into larger, multilamellar structures and promotes fusion. Unger's composition comprises a charged lipid, a counter ion, a lipid covalently bonded to a polymer, and a bioactive agent. See column 2, lines 20-30. The composition is in the form of a vesicle including liposomes and micelles, which can be solid or porous. See column 4, lines 19-45. The vesicles preferably have diameters of less than about 30 microns and more preferably less than about 12 microns. See column 68, lines 1-6. The charged lipid may be anionic (i.e., negatively charged, that is, carrying a net negative charge) or cationic (i.e., positively charged, that is, carrying a net positive charge). See column 11, lines 5-10. A cationic counter ion is used to form the compositions. Preferred cations are **calcium**, magnesium, and zinc, and paramagnetic cations such as manganese and gadolinium. Most preferably the cation is calcium. See column 12, lines 1-5. Specifically, example 2 teaches the composition comprising instantly claimed dipalmitoylphosphatidylcholine (**DPPC**), dipalmitoylphosphatidic acid

(DPPA), dipalmitoylphosphatidylethanolamine-polyethylene glycol-5,000 (DPPE-PEG5,000), and calcium chloride. Example 13 discloses lyophilizing the composition of example 2 to yield a dry powder. Unger teaches the lipid covalently bonded to a polymer (e.g., DPPE-PEG-5,000) causes compaction of the size of the composition in the presence of a counter ion, such as calcium, when compared to the corresponding compositions that do not contain a counter ion. The compaction effect caused by the lipid covalently bonded to the polymer is most notable when the counter ion is added at the initial incubation of the lipid mixture. Increasing the amount of the lipid covalently bonded to a polymer allows the composition to stabilize in the presence of a counter ion. When the lipid covalently bonded to the polymer is present in an amount less than about 5%, the composition is generally unstable and may precipitate. See column 10, lines 50-55. Unger discloses the lipid composition is useful for delivering bioactive agents to a patient's lungs. For pulmonary applications, dried or lyophilized powdered compositions are administered via an inhaler.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Hanes and Unger and utilize calcium in the microstructures of Hanes. One would have been motivated to utilize calcium in the formation of Hanes's particles since Unger teaches the use of cations such as calcium, which promotes fusion of the phospholipids and stabilizes compaction of phospholipid-polymer containing particles, specifically in a PEG-phospholipid particle. Further, a skilled artisan would have expected the same stabilizing effect in Hanes's particles since Hanes also teaches a particle comprising PEG and a phospholipid.

With regard to porosity, pore size, and shell thickness, although Hanes does not specify the porosity in terms of weight percent as instantly claimed, specify the pore size, or the shell thickness, it is the examiner's position that the Hanes would have a similar porosity, pore size, and shell thickness as instantly claimed for the following reason: Hanes teaches a substantially similar particle with instant bulk density (measured by tap density), instant geometric diameter, and instant aerodynamic diameter. Thus, "when a structure recited in the reference is substantially identical to that of the claims, claimed properties are presumed to be the inherent". See MPEP 2112.01. Further, Hanes teaches the porous and light nature of the microstructure contributes to the properties such as the low tap density of the particle and Hanes teaches the same density as claimed; thus the pore size and porosity must be similar as instantly claimed. Further, since the shell thickness also would contribute to the density of the particles and the prior art teaches the same density as claimed, it is the examiner's position that the prior art would have the same shell thickness as claimed. It should be noted that the examiner has provided a rationale as to why Hanes's particle would have the same or similar porosity, pore size, and shell thickness; thus the burden has shifted to the applicant to provide evidence to the contrary. See MPEP 2112.

Furthermore, assuming arguendo that Hanes's porosity, pore size, and shell thickness are not the same as instantly claimed, the manipulation of these parameters is considered prima facie obvious to one of ordinary skill in the art since Hanes provides the guidance in which the various factors can be manipulated (column 9 and examples) to yield the desired property. For instance, Hanes teaches manipulating the outlet and

inlet temperature when making the particles to manipulate the porosity. Further, Hanes teaches the manipulation of surface roughness (porosity), diameter, and tap density to determine the delivery site of the particles in the lungs (lower lung region or upper lung region). (col. 8, lines 19-68 and column 9). Therefore, a skilled artisan would have been motivated to look at the guidance of Hanes and manipulate the above factors and fabricate the microstructure according to the lung region to be targeted.

Response to Arguments

In the request for continued examination filed 4/6/09, applicant did not present any new arguments. As such, the arguments pertaining to the response of 12/5/08 are reiterated below.

Applicant argues that Hanes and Unger do not render independent claims 57 and 80 as amended, unpatentable. According to applicant, Hanes does not teach particulate microstructures that comprise greater than about 50% phospholipid. Applicant argues that Hanes teaches particles that are primarily composed of polymer in columns 5 and 6. Applicant believes that Unger does not make up for the deficiency in Hanes. Furthermore, applicant argues that the motivation provided by the examiner for incorporating the calcium of Unger was based on the calcium's interaction with the polymer. Applicant believes that the motivation would not exist if the particles were primarily phospholipid. Applicant argues that the examiner has failed to establish that the teachings of Unger could be applied, with a reasonable likelihood of success to Hanes et al. Applicant states that the invention set forth in claims 57 and 80 was

unexpected and is particularly useful for delivering an active agent to the lungs in a reproducible manner.

In response to applicant's arguments, Hanes does teach microparticulates that comprise greater than about 50% phospholipid. In table 4, Hanes teaches that DPPC is loaded in the spheres at weight percents of 62.8 and 89.1 (column 18, lines 35-50). Therefore, Hanes still reads on the amended independent claims 57 and 80.

Applicant argues that Hanes teaches that the phospholipids may be formed solely of the drug and surfactant. Thus, this is a teaching away from the use of calcium.

The examiner disagrees that Hanes teaches that if the microstructure is made of the surfactant, then it can only be made of the surfactant and active. Hanes teaches that the microstructures can be made of a polymer, drug, and surfactant or alternatively the microstructure can be of the surfactant and drug. This is different from a teaching that it can only be made of a surfactant and drug. Hanes's context is directed to excluding the polymer and not excipients that facilitate the method of making the microstructure. Unger clearly teaches the use of counter ions such as calcium in the formation of a microstructure and Hanes teaches "Particles may be made using methods for making microspheres or microcapsules known in the art."

In addition, Unger provides further motivation to incorporate a higher amount of lipid. According to Unger, increasing the amount of the lipid covalently bonded to a polymer allows the composition to stabilize in the presence of a counter ion. As described above, the counter ion or calcium is used to promote fusion and to "fuse" the lipid components to form a stable vesicle. Calcium is used to fuse the lipid components

to form the particle itself because the invention of Unger is directed to the calcium ions as part of the structural matrix and not part of the external environment. Unger teaches that when the lipid covalently bonded to the polymer is present in an amount of less than about 5%, the composition is generally unstable and may precipitate (column 10, lines 61-67). Therefore, it would have been obvious to an artisan of ordinary skill at the time the invention was made to have a higher amount of phospholipid in the composition of Hanes et al because it allows the composition to stabilize in the presence of a counter ion. Furthermore, one would have been motivated to use more than 5% phospholipid to prevent the composition from precipitating.

Furthermore, the examiner respectfully disagrees with applicant that motivation to combine Hanes with Unger would not exist if the particles were primarily phospholipid. First, the motivation provided by the examiner for incorporating the calcium of Unger was based on the calcium's interaction with the **polymer-phospholipid** not just the polymer as argued by applicant. Second, Hanes does not teach 100 wt.% phospholipid. Hanes only teaches 62.8 and 89.1, which allows for polymer to still be incorporated within the particle. According to Hanes, the particles can be formed from any biocompatible and preferably biodegradable polymer, copolymer or blend. Moreover, applicant themselves stated on the record that Hanes teaches particles that are primarily composed of polymer. Therefore, the motivation to combine Hanes with Unger still exists. Since Unger teaches the use of cations such as calcium, which promotes fusion of the phospholipids and stabilizes compaction of phospholipid-polymer containing particles specifically in a PEG-phospholipid particle,

one would have been motivated with a reasonable expectation of success to incorporate calcium in the microstructures of Hanes. Further, a skilled artisan would have expected the same stabilizing effect in Hanes's particles since Hanes also teaches a particle comprising PEG and a phospholipid.

Finally, regarding applicant's argument of unexpectedly finding that the claimed invention is particularly useful for delivering an active agent to the lungs in a reproducible manner, Hanes teaches a plurality of particles used for delivering active agents to the lungs. Hanes teaches that the particles may be prepared using single and double emulsion solvent evaporation, spray drying, solvent extraction, etc and any other methods for making microspheres or microcapsules known in the art (column 6, lines 61-67). Therefore, like the claimed invention, Hanes also teaches the delivery of an active agent to the lungs in a reproducible manner. According to MPEP 2145, a showing of unexpected results must be based on evidence, not just mere arguments or speculation. *In re Mayne, 104 F.3d 1339, 1343-44, 41 USPQ2d 1451, 1455-56 (Fed. Cir. 1997)* (conclusory statements that claimed compound possesses unusually low immune response or unexpected biological activity that is unsupported by comparative data held insufficient to overcome prima facie case of obviousness). Since Hanes teaches a plurality of particles that can be formed in a reproducible manner, applicant's argument claiming unexpected results is not found persuasive. It is the position of the examiner, that there is proper motivation to combine Hanes and Unger and render the claims as amended obvious.

Claims 78 and 101 are under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5855913) in view of Unger (6,120,751) as evidenced by 5,776,488 in further view of Igarashi et al (4201774).

The detailed teachings of Hanes and Unger have been set forth above. Hanes et al teach dry powder inhaler compositions. Hanes teaches several active agents including antibiotics in the composition. Unger teaches the use of calcium to stabilize the phospholipids.

Hanes does not teach the specific use of aminoglycoside antibiotic.

Igarashi et al teaches aminoglycoside antibiotics for the treatment of gram-positive and gram-negative bacteria.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the instant medicament in Hanes et al's composition. One would be motivated to do so since the instant antibiotics treat gram-positive and gram-negative bacteria and depending on the patient's requirement, the appropriate drug is used. One would have expected similar results since Hanes teaches the suitability of antibiotics as the active agent. Therefore, the selection of a particular drug for use in the composition is considered prima facie obvious since the selection depends on the symptoms and disease being treated.

Response to Arguments

In the request for continued examination filed 4/6/09, applicant did not present any new arguments. As such, the arguments pertaining to the response of 12/5/08 are reiterated below.

Applicant only argues that Igarashi does not cure the deficiencies of Hanes and Unger. Applicant believes that the claims are allowable for the reason that they depend from allowable claims.

The merits of Hanes and Unger have been discussed above and are incorporated herein. The rejection of Hanes in view of Unger is maintained and thus the dependent claims are not allowable. Igarashi is only relied upon to teach the instant aminoglycoside antibiotic as an active agent, which applicant has not addressed.

Thus, it is the examiner's position that Hanes in view of Unger and in further view of Igarashi renders the claims as amended obvious.

Claims 79 and 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5855913) in view of Unger (6,120,751) as evidenced by 5,776,488 in further view of Benson et al (5,006,343).

The detailed teachings of Hanes and Unger have been set forth above. Hanes et al teach dry powder inhaler compositions. Hanes teaches several active agents including antibiotics in the composition. Unger teaches the use of calcium to stabilize the phospholipids.

Hanes does not teach the specific use of fungicides.

Benson et al teach pulmonary administration of active agents to treat pulmonary diseases. Suitable drugs that may be administered for lung specific disease include fungicides. See column 10, lines 33-45.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a fungicide in Hanes et al's composition. One would be motivated to do so since Benson et al teach the use of array of medications including fungicides that are useful for treating lung diseases. Therefore, the selection of a particular drug for use in the composition is considered prima facie obvious since the selection depends on the symptoms and disease being treated.

Response to Arguments

In the request for continued examination filed 4/6/09, applicant did not present any new arguments. As such, the arguments pertaining to the response of 12/5/08 are reiterated below.

Applicant only argues that Benson does not cure the deficiencies of Hanes and Unger. Applicant believes that the claims are allowable for the reason that they depend from allowable claims.

The merits of Hanes and Unger have been discussed above and are incorporated herein. The rejection of Hanes in view of Unger is maintained and thus the dependent claims are not allowable. Benson is only relied upon to teach the instant fungicide as an active agent, which applicant has not addressed.

Thus, it is the examiner's position that Hanes in view of Unger and in further view of Benson renders the claims as amended obvious.

Claims 57, 59-77, 80, 82-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5,855,913) in view of Mathiowitz et al (6,248,720) or Cohen et al (5149543) respectively as evidenced by 5,776,488. Note US '488 is only relied upon to show the inherent property claimed in claims 72, 80, and 95.

Hanes et al teach aerodynamically light particles for drug delivery to the pulmonary system. The particles have a tap density of less than 0.4 g/cm3, aerodynamic diameter of 3 microns (see column 9, line 45-50), and a mass mean diameter (geometric diameter) between 5 to 30 microns. See abstract, See column 9, lines 26-45, and claim 1. Claim 3 teaches a tap density of less than 0.1 g/cm3. Table 2 teaches the porous microparticles with DPPC (phospholipids) have a density of 0.30 g/cm3. It should be noted that Hanes teaches tap density is a standard measure of the envelope mass density (bulk density) on column 9, lines 5-6. On column 14, lines 36-40, Hanes teaches the bulk density is estimated by tap density measurements.

Hanes teaches the presence of irregular surface structure, or pores or cavities within the particle (this reads on instantly claimed "hollow microstructure") contributes to the aerodynamic lightness. Hanes also teaches the irregular surface texture and porous structure also contributes to the low tap density and manipulation of these features permits the delivery of larger particle envelope volumes into the lungs (col. 9, lines 10-

25). Porosity and surface roughness can be increased by varying the inlet and outlet temperatures, among other factors. See column 12, lines 10-13. The aerodynamically light particles may be fabricated to provide a particle sample with a preselected size distribution. For example, greater than 30%, 50%, 70%, or 80% of the particles in a sample can have a geometric diameter within a selected range of at least 5 microns. The particles contain surfactants such as DPPC (instant gel to liquid temperature; see US 5,776,488 as art of interest) and the microstructures are taught to encapsulate active agents, which allow the active to remain protected (col. 10, lines 37-50 and examples). Note that DPPC is a zwitterionic lipid and is present in an amount of 62.8 wt.% and 89.1 wt.% in Table 4 of Hanes (column 18, lines 35-50). The particles can also be co-delivered with larger carrier particles, not carrying a therapeutic agent, having, for example, a mean diameter ranging between about 50 microns and 100 microns. See column 4, lines 12-15.

Biodegradable polymer, copolymers, or a blend may be utilized. Hanes teaches the use of polyglycolic acid and polylactic acid with a surfactant (DPPC) and the polyester may also have charged or functionizable groups such as amino acids. Other polymers taught are acrylic acids and methacrylic acids and polyvinyl compounds may be used to make the microsphere. See column 5, line 49 to column 6, line 27. Further, the particles may be formed into microspheres by various methods including but not limited to **coacervation (note a coacervate is a spherical aggregation of lipid molecules)**, interfacial polymerization, etc. (note col. 6). Instant therapeutic agents including insulin, growth hormones, etc. are taught on column 10, lines 4-30.

Hanes teaches aerodynamically light PEG particles were prepared by spray drying using 5 g PEG (MW 15,000-20,000, Sigma) and the surfactant such as DPPC may be incorporated into the polymer solution prior to particle formation, or optionally the particles can be ionically or covalently coated by surfactant on the particle surface after particle formation, or the surfactant may be absorbed onto the particle surface. See column 13, lines 1-25.

Hanes et al do not teach the use of calcium in the structural matrix.

Mathiowitz teaches polymeric microparticles for administration by inhalation. See abstract and column 4, lines 10-42. Mathiowitz teaches making nanospheres and microspheres in the range of 10 nm to 10 microns. See column 7, lines 50-55. Mathiowitz teaches various biodegradable polymers including the polymers taught by Hanes. See column 11, lines 30-50 and Table 1. Mathiowitz teaches the bioadhesive properties of a polymer are enhanced by incorporating a metal compound into the polymer to enhance the ability of the polymer to adhere to a tissue surface such as a mucosal membrane. Metal compounds which enhance the bioadhesive properties of a polymer preferably are water-insoluble metal compounds, such as water-insoluble metal oxides and hydroxides. The water-insoluble metal compounds, such as metal oxides, can be incorporated by one of the following mechanisms: (a) physical mixtures which result in entrapment of the metal compound; (b) ionic interaction between metal compound and polymer; (c) surface modification of the polymers which would result in exposed metal compound on the surface; and (d) coating techniques such as fluidized bead, pan coating or any similar methods known to those skilled in the art, which

produce a metal compound enriched layer on the surface of the device. The water-insoluble metal compounds can be derived from metals including **calcium**, iron, copper, zinc, cadmium, zirconium and titanium. See column 13, lines 20-51.

Cohen et al teach a method of making microspheres. The method is based on the use of water-soluble polymers with charged sides that are crosslinked with multivalent cations (abstract). Suitable polymers that are reacted with cations are polyacrylic acids, polymethacrylic acid, PCPP, polyvinyl compounds, etc (col. 4, lines 1-5). The cations taught are calcium, copper, magnesium, etc (col. 6, line 22). A typical example for microsphere preparation utilizes polymer and calcium chloride concentrations of 2.5% and 7.5% (w/v). Microspheres are prepared by spraying an aqueous solution of polymer containing the entity of interest, using a droplet-forming apparatus.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Hanes and Mathiowitz and utilize calcium in the microstructures of Hanes. One would have been motivated to utilize calcium in the formation of Hanes's particles since Mathiowitz teaches the use of water-insoluble metal compounds derived from calcium, iron, copper, etc, enhance bioadhesive properties of the polymer to allow the microspheres to adhere to tissue surface such as mucosal surfaces. Therefore, a skilled artisan would have been motivated to add compounds such as calcium to increase the bioadhesive properties of the microparticles. Moreover, a skilled artisan would have reasonably expected success since Hanes teaches polymeric-phospholipid microparticles for inhalation and thus one

would have desired to increase the adherence of the particles to the respiratory mucosa.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Hanes and Cohen since Cohen teaches the method of making microspheres through interfacial polymerization using cations such as calcium. One would be motivated to do so with the expectation of similar results since Hanes teaches the use of polymers with charged sides such as polyacrylic acids, etc. and teaches that any process of making the microsphere is suitable including interfacial polymerization.

With regard to the claims 4-5 (porosity), claims 6-7 (pore size), and claim 13 (shell thickness), although Hanes does not specify the porosity in terms of weight percent as instantly claimed, specify the pore size, or the shell thickness, it is the examiner's position that the Hanes would have a similar porosity, pore size, and shell thickness as instantly claimed for the following reason: Hanes teaches a substantially similar particle with instant bulk density (measured by tap density), instant geometric diameter, and instant aerodynamic diameter. Thus, "when a structure recited in the reference is substantially identical to that of the claims, claimed properties are presumed to be the inherent". See MPEP 2112.01. Further, Hanes teaches the porous and light nature of the microstructure contributes to the properties such as the low tap density of the particle and Hanes teaches the same density as claimed; thus the pore size and porosity must be similar as instantly claimed. Further, since the shell thickness also would contribute to the density of the particles and the prior art teaches the same

density as claimed, it is the examiner's position that the prior art would have the same shell thickness as claimed. It should be noted that the examiner has provided a rationale as to why Hanes's particle would have the same or similar porosity, pore size, and shell thickness; thus the burden has shifted to the applicant to provide evidence to the contrary. See MPEP 2112.

Furthermore, assuming arguendo that Hanes's porosity, pore size, and shell thickness are not the same as instantly claimed, the manipulation of these parameters is considered prima facie obvious to one of ordinary skill in the art since Hanes provides the guidance in which the various factors can be manipulated (column 9 and examples) to yield the desired property. For instance, Hanes teaches manipulating the outlet and inlet temperature when making the particles to manipulate the porosity. Further, Hanes teaches the manipulation of surface roughness (porosity), diameter, and tap density to determine the delivery site of the particles in the lungs (lower lung region or upper lung region). (col. 8, lines 19-68 and column 9). Therefore, a skilled artisan would have been motivated to look at the guidance of Hanes and manipulate the above factors and fabricate the microstructure according to the lung region to be targeted.

Response to Arguments

In the request for continued examination filed 4/6/09, applicant did not present any new arguments. As such, the arguments pertaining to the response of 12/5/08 are reiterated below.

Applicant argues that Hanes and Mathiowitz or Cohen do not render independent claims 57 and 80 as amended, unpatentable. According to applicant, Hanes does not teach particulate microstructures that comprise greater than about 50% phospholipid. Applicant argues that Hanes teaches particles that are primarily composed of polymer in columns 5 and 6. Applicant believes that Mathiowitz and Cohen both teach polymeric particles and do not make up for the deficiency in Hanes. Furthermore, applicant argues that there is no motivation for incorporating the calcium of Mathiowitz or Cohen with the particles of Hanes. Applicant argues that the examiner has failed to establish that the teachings of Mathiowiz or Cohen could be applied, with a reasonable likelihood of success to Hanes et al. Applicant states that the invention set forth in claims 57 and 80 was unexpected and is particularly useful for delivering an active agent to the lungs in a reproducible manner.

In response to applicant's arguments, Hanes does teach microparticulates that comprise greater than about 50% phospholipid. In table 4, Hanes teaches that DPPC is loaded in the spheres at weight percents of 62.8 and 89.1 (column 18, lines 35-50). Therefore, Hanes still reads on the amended independent claims 57 and 80.

Furthermore, the examiner respectfully disagrees with applicant that there is no motivation to combine Hanes with Mathiowitz or Cohen. It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Hanes and Mathiowitz and utilize calcium in the microstructures of Hanes. One would have been motivated to utilize calcium in the formation of Hanes's particles since Mathiowitz teaches the use of water-insoluble metal compounds derived from

calcium, iron, copper, etc, enhance bioadhesive properties of the polymer to allow the microspheres to adhere to tissue surface such as mucosal surfaces. Therefore, a skilled artisan would have been motivated to add compounds such as calcium to increase the bioadhesive properties of the microparticles. Moreover, a skilled artisan would have reasonably expected success since Hanes teaches polymeric-phospholipid microparticles for inhalation and thus one would have desired to increase the adherence of the particles to the respiratory mucosa.

Finally, regarding applicant's argument of unexpectedly finding that the claimed invention is particularly useful for delivering an active agent to the lungs in a reproducible manner, Hanes teaches a plurality of particles used for delivering active agents to the lungs. Hanes teaches that the particles may be prepared using single and double emulsion solvent evaporation, spray drying, solvent extraction, etc and any other methods for making microspheres or microcapsules known in the art (column 6, lines 61-67). Therefore, like the claimed invention, Hanes also teaches the delivery of an active agent to the lungs in a reproducible manner. According to MPEP 2145, a showing of unexpected results must be based on evidence, not just mere arguments or speculation. *In re Mayne, 104 F.3d 1339, 1343-44, 41 USPQ2d 1451, 1455-56 (Fed. Cir. 1997)* (conclusory statements that claimed compound possesses unusually low immune response or unexpected biological activity that is unsupported by comparative data held insufficient to overcome prima facie case of obviousness). Since Hanes teaches a plurality of particles that can be formed in a reproducible manner, applicant's argument claiming unexpected results is not found persuasive.

Thus, it is the position of the examiner, that there is proper motivation to combine Hanes with Mathiowitz or Cohen and render the claims as amended obvious.

Claims 57, 59-77, 80, 82-100 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5,855,913) in view of Papahadjopoulos et al (Cochleate lipid cylinders: Formation by fusion of unilamellar lipid vesicles, Biochimica et Biophysics, 394 (1975), 483-491) as evidenced by 5,776,488. Note US '488 is only relied upon to show the inherent property claimed in claims 72 and 95.

Hanes et al teach aerodynamically light particles for drug delivery to the pulmonary system. The particles have a tap density of less than 0.4 g/cm3, aerodynamic diameter of 3 microns (see column 9, line 45-50), and a mass mean diameter (geometric diameter) between 5 to 30 microns. See abstract, See column 9, lines 26-45, and claim 1. Claim 3 teaches a tap density of less than 0.1 g/cm3. Table 2 teaches the porous microparticles with DPPC (phospholipids) have a density of 0.30 g/cm3. It should be noted that Hanes teaches tap density is a standard measure of the envelope mass density (bulk density) on column 9, lines 5-6. On column 14, lines 36-40, Hanes teaches the bulk density is estimated by tap density measurements.

Hanes teaches the presence of irregular surface structure, or pores or cavities within the particle (this reads on instantly claimed "hollow microstructure") contributes to the aerodynamic lightness. Hanes also teaches the irregular surface texture and porous structure also contributes to the low tap density and manipulation of these features

permits the delivery of larger particle envelope volumes into the lungs (col. 9, lines 10-25). Porosity and surface roughness can be increased by varying the inlet and outlet temperatures, among other factors. See column 12, lines 10-13. The aerodynamically light particles may be fabricated to provide a particle sample with a preselected size distribution. For example, greater than 30%, 50%, 70%, or 80% of the particles in a sample can have a geometric diameter within a selected range of at least 5 microns. The particles contain surfactants such as DPPC (instant gel to liquid temperature; see US 5,776,488 as art of interest) and the microstructures are taught to encapsulate active agents, which allow the active to remain protected (col. 10, lines 37-50 and examples). Note that DPPC is a zwitterionic lipid and is present in an amount of 62.8 wt.% and 89.1 wt.% in Table 4 of Hanes (column 18, lines 35-50). The particles can also be co-delivered with larger carrier particles, not carrying a therapeutic agent, having, for example, a mean diameter ranging between about 50 microns and 100 microns. See column 4, lines 12-15.

Biodegradable polymer, copolymers, or a blend may be utilized. Hanes teaches the use of polyglycolic acid and polylactic acid with a surfactant (DPPC) and the polyester may also have charged or functionizable groups such as amino acids. Other polymers taught are acrylic acids and methacrylic acids and polyvinyl compounds may be used to make the microsphere. See column 5, line 49 to column 6, line 27. Further, the particles may be formed into microspheres by various methods including but not limited to **coacervation (note a coacervate is a spherical aggregation of lipid**

molecules), interfacial polymerization, etc. (note col. 6). Instant therapeutic agents including insulin, growth hormones, etc. are taught on column 10, lines 4-30.

Hanes teaches aerodynamically light PEG particles were prepared by spray drying using 5 g PEG (MW 15,000-20,000, Sigma) and the surfactant such as DPPC may be incorporated into the polymer solution prior to particle formation, or optionally the particles can be ionically or covalently coated by surfactant on the particle surface after particle formation, or the surfactant may be absorbed onto the particle surface. See column 13, lines 1-25.

Hanes et al do not teach the use of calcium in the structural matrix.

Papahadjopoulos et al teaches adding calcium to fuse phospholipids including the phospholipids taught by Hanes into larger vesicles. The reference teaches small vesicles with a size of 200-500 A in diameter can be made into bigger vesicles of a size of 0.2-1 micron. The reference teaches using calcium to form the desired size of the vesicle. See abstract.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Hanes and Papahadjopoulos and utilize calcium. One would be motivated to do so with the expectation of similar results since Hanes teaches the use of phospholipids only to form the particles and Papahadjopoulos teaches the use of calcium provides the desired vesicle size. Therefore, a skilled artisan would have been motivated to use the desired concentration of calcium to provide the desired lipid vesicles size. Note that the amount of calcium used provides the desired size as taught by Papahadjopoulos. Papahadjopoulos

teaches forming bigger vesicles of a size of 0.2-1 microns in diameter and applicant claims a size of 1-30 microns.

With regard to the claims 4-5 (porosity), claims 6-7 (pore size), and claim 13 (shell thickness), although Hanes does not specify the porosity in terms of weight percent as instantly claimed, specify the pore size, or the shell thickness, it is the examiner's position that the Hanes would have a similar porosity, pore size, and shell thickness as instantly claimed for the following reason: Hanes teaches a substantially similar particle with instant bulk density (measured by tap density), instant geometric diameter, and instant aerodynamic diameter. Thus, "when a structure recited in the reference is substantially identical to that of the claims, claimed properties are presumed to be the inherent". See MPEP 2112.01. Further, Hanes teaches the porous and light nature of the microstructure contributes to the properties such as the low tap density of the particle and Hanes teaches the same density as claimed; thus the pore size and porosity must be similar as instantly claimed. Further, since the shell thickness also would contribute to the density of the particles and the prior art teaches the same density as claimed, it is the examiner's position that the prior art would have the same shell thickness as claimed. It should be noted that the examiner has provided a rationale as to why Hanes's particle would have the same or similar porosity, pore size, and shell thickness; thus the burden has shifted to the applicant to provide evidence to the contrary. See MPEP 2112.

Furthermore, assuming arguendo that Hanes's porosity, pore size, and shell thickness are not the same as instantly claimed, the manipulation of these parameters

is considered prima facie obvious to one of ordinary skill in the art since Hanes provides the guidance in which the various factors can be manipulated (column 9 and examples) to yield the desired property. For instance, Hanes teaches manipulating the outlet and inlet temperature when making the particles to manipulate the porosity. Further, Hanes teaches the manipulation of surface roughness (porosity), diameter, and tap density to determine the delivery site of the particles in the lungs (lower lung region or upper lung region). (col. 8, lines 19-68 and column 9). Therefore, a skilled artisan would have been motivated to look at the guidance of Hanes and manipulate the above factors and fabricate the microstructure according to the lung region to be targeted.

Response to Arguments

In the request for continued examination filed 4/6/09, applicant did not present any new arguments. As such, the arguments pertaining to the response of 12/5/08 are reiterated below.

Applicant argues that Hanes and Papahadjopoulos do not render independent claims 57 and 80 as amended, unpatentable. According to applicant, Hanes does not teach particulate microstructures that comprise greater than about 50% phospholipid. Applicant argues that Hanes teaches particles that are primarily composed of polymer in columns 5 and 6. Applicant believes that Papahadjopoulos teaches polymeric particles and does not make up for the deficiency in Hanes. Furthermore, applicant argues that there is no motivation for incorporating the calcium of Papahadjopoulos with the particles of Hanes. Applicant argues that the examiner has failed to establish that the

teachings could be applied, with a reasonable likelihood of success to Hanes. Applicant states that the invention set forth in claims 57 and 80 was unexpected and is particularly useful for delivering an active agent to the lungs in a reproducible manner.

In response to applicant's arguments, Hanes does teach microparticulates that comprise greater than about 50% phospholipid. In table 4, Hanes teaches that DPPC is loaded in the spheres at weight percents of 62.8 and 89.1 (column 18, lines 35-50). Therefore, Hanes still reads on the amended independent claims 57 and 80.

Furthermore, the examiner respectfully disagrees with applicant that there is no motivation to combine Hanes with Papahadjopoulos. It would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Hanes and Papahadjopoulos and utilize calcium. One would be motivated to do so with an expectation of similar results since Hanes teaches the use of phospholipids to form particles and Papahadjopoulos teaches the use of calcium provides the desired vesicle size. Therefore, a skilled artisan would have been motivated to use the desired concentration of calcium to provide the desired lipid vesicle size.

Finally, regarding applicant's argument of unexpectedly finding that the claimed invention is particularly useful for delivering an active agent to the lungs in a reproducible manner, Hanes teaches a plurality of particles used for delivering active agents to the lungs. Hanes teaches that the particles may be prepared using single and double emulsion solvent evaporation, spray drying, solvent extraction, etc and any other methods for making microspheres or microcapsules known in the art (column 6, lines 61-67). Therefore, like the claimed invention, Hanes also teaches the delivery of an

active agent to the lungs in a reproducible manner. According to MPEP 2145, a showing of unexpected results must be based on evidence, not just mere arguments or speculation. *In re Mayne, 104 F.3d 1339, 1343-44, 41 USPQ2d 1451, 1455-56 (Fed. Cir. 1997)* (conclusory statements that claimed compound possesses unusually low immune response or unexpected biological activity that is unsupported by comparative data held insufficient to overcome prima facie case of obviousness). Since Hanes teaches a plurality of particles that can be formed in a reproducible manner, applicant's argument claiming unexpected results is not found persuasive.

Thus, it is the position of the examiner, that there is proper motivation to combine Hanes with Papahadjopoulos and render the claims as amended obvious.

Claims 78 and 101 are under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5855913) in view of Mathiowitz et al (6,248,720) or Cohen et al (5149543) or Papahadjopoulos et al (Cochleate lipid cylinders: Formation by fusion of unilamellar lipid vesicles, Biochimica et Biophysics, 394 (1975), 483-491) *respectively* as evidenced by 5,776,488 in further view of Igarashi et al (4201774).

The detailed teachings of Hanes, Mathiowitz, Cohen, and Papahadjopoulos have been set forth above. Hanes et al teach dry powder inhaler compositions. Hanes teaches several active agents including antibiotics in the composition.

Hanes does not teach the specific use of aminoglycoside antibiotic.

Igarashi et al teaches aminoglycoside antibiotics for the treatment of gram-positive and gram-negative bacteria.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the instant medicament in Hanes' composition. One would be motivated to do so since the instant antibiotics treat gram-positive and gram-negative bacteria and depending on the patient's requirement, the appropriate drug is used. One would have expected similar results since Hanes teaches the suitability of antibiotics as the active agent. Therefore, the selection of a particular drug for use in the composition is considered prima facie obvious since the selection depends on the symptoms and disease being treated.

Response to Arguments

In the request for continued examination filed 4/6/09, applicant did not present any new arguments. As such, the arguments pertaining to the response of 12/5/08 are reiterated below.

Applicant only argues that Igarashi does not cure the deficiencies of Hanes and Papahadjopoulos. Applicant believes that the claims are allowable for the reason that they depend from allowable claims.

The merits of Hanes, Papahadjopoulos, Mathiowitz, and Cohen have been discussed above and are incorporated herein. The rejections of Hanes in view of Papahadjopoulos, Mathiowitz, or Cohen are maintained and thus the dependent claims are not allowable.

Igarashi is only relied upon to teach the instant aminoglycoside antibiotic as an active agent, which applicant has not addressed.

Thus, it is the examiner's position that Hanes in view of Papahadjopoulos, Mathiowitz, or Cohen and in further view of Igarashi renders the claims as amended obvious.

Claims 79 and 102 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hanes et al (US 5855913) in view of Mathiowitz et al (6,248,720) or Cohen et al (5149543) or Papahadjopoulos et al (Cochleate lipid cylinders: Formation by fusion of unilamellar lipid vesicles, Biochimica et Biophysics, 394 (1975), 483-491) *respectively* as evidenced by 5,776,488 in further view of Benson et al (5,006,343).

The detailed teachings of Hanes, Mathiowitz, and Cohen have been set forth above. Hanes et al teach dry powder inhaler compositions. Hanes teaches several active agents including antibiotics in the composition.

Hanes does not teach the specific use of fungicides.

Benson et al teach pulmonary administration of active agents to treat pulmonary diseases. Suitable drugs that may be administered for lung specific disease include fungicides. See column 10, lines 33-45.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use a fungicide in Hanes et al's composition. One would be motivated to do so since Benson et al teach the use of array of medications including fungicides that are useful for treating lung diseases. Therefore, the selection of a

particular drug for use in the composition is considered prima facie obvious since the selection depends on the symptoms and disease being treated.

Response to Arguments

In the request for continued examination filed 4/6/09, applicant did not present any new arguments. As such, the arguments pertaining to the response of 12/5/08 are reiterated below.

Applicant presents no arguments for this rejection.

Thus, it is the examiner's position that Hanes in view of Papahadjopoulos, Mathiowitz, or Cohen and in further view of Benson renders the claims as amended obvious.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 57, 59-80, 82-102 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 8-9, 11-15, 17, 19-25, 29-32, 53-55, 57-62, 64-66, 67-89 of Application No. 09/851226 (now US Patent 7,442,388).

The instant application is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix, with a geometric diameter of 1-30 microns, a bulk density of less than about 0.5 g/cm3, and an aerodynamic diameter of less than 5 microns. The claims are also directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix wherein said phospholipids comprises a gel to liquid crystal transition temperature of greater than 40 degrees Celsius. Dependent claims are directed to active agents selected from antiinflammatories, lung surfactants, antibiotics, antineoplastics, antifungals, specifically insulin, growth factors etc. The phospholipid is selected from dilauroylphosphatidylcholine, dioleylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, dibehenoylphosphatidylcholine, and diarachidoylphosphatidylcholine, and combinations.

‘226 is directed to a particulate composition comprising an active agent, a saturated phospholipid, and a polyvalent cation, wherein the ratio of the polyvalent cation to phospholipid is at least 0.05 and is sufficient high to increase the gel-to-liquid crystal transition temperature of the particles without the cation. Dependent claims are directed to calcium as the metal ion. Dependent claim is directed to a gel to liquid crystal transition temperature of greater than 40 degrees Celsius. Dependent claims are

directed to the same active agent insulin and growth hormones. Dependent claims are directed to a mass median diameter of 0.5-5 microns, an aerodynamic diameter of 0.5-5 microns, and a bulk density of less than 0.5 and 0.05 respectively. The phospholipid is selected from dipalmitoylphosphatidylcholine and disteroylphosphatidylcholine.

The instant application and '226 are different in that '226 is directed to the broad scope of the metal ion and the instant application is directed to the metal ion species calcium; however, '226 claims calcium in the dependent claims. Further, '226 claims the amount of the cation to increase the gel to liquid transition temperature and the instant application does not recite any concentration of the cation. However, the manipulation of concentrations is considered to be prima facie obvious. See In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). Thus, the instant application and copending application have overlapping subject matter wherein both applications are directed to microparticles comprising the critical elements of 1) an active agent, 2) a phospholipid, and 3) a metal ion.

Claims 57, 59-80, 82-102 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-7, 9-10, 46-50, 54-57, 59, 61-67, 69-70, 74-77, 79-90 of copending Application No. 09/568818. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

The instant application claim 39 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix,

with a geometric diameter of 1-30 microns, a bulk density of less than about 0.5 g/cm3, and an aerodynamic diameter of less than 5 microns. Independent claim 40 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix wherein said phospholipids comprises a gel to liquid crystal transition temperature of greater than 40 degrees Celsius. Dependent claims are directed to active agents selected from antiinflammatories, lung surfactants, antibiotics, antifungals, insulin, etc. The phospholipid is selected from dilauroylphosphatidylcholine, dioleylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, dibehenoylphosphatidylcholine, and diarachidoylphosphatidylcholine, and combinations.

Copending independent claims 46, 59, and 82 are directed to a microparticle comprising an active agent and a metal-ion complex with a density as measured by He displacement is 0.5-2 g/ml. Calcium is one of the metal ion species claimed in a dependent claim. Dependent claims are directed to phospholipids and specifically selected from the group comprising “dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, and dimyristylphosphatidylcholine”. Dependent claims are directed to the same active agents as claimed in instant application. Dependent claims are directed to an aerodynamic particle size of 0.5-7 microns. Dependent claims are directed to dry powder. Dependent claim are directed to a zwitterionic lipid.

The instant application and ‘818 are different in that firstly ‘818 independent claims do not recite a phospholipid; however the dependent claims further comprise phospholipids, more specifically, the instant phospholipids. Thus, the instant application

and copending application have overlapping subject matter wherein both applications are directed to microparticles comprising the critical elements of 1) an active agent, 2) a phospholipid, and 3) a metal ion. Secondly, '818 is directed to the broad scope of the metal ion and the instant application is directed to the metal ion species calcium; however, '818 claims calcium in the dependent claims. Further, '818 is broadly directed to microparticles without claiming the density, the geometric diameter, pore size, etc.; however '818 encompasses the scope of the instant microstructures and the respective properties, which is the narrower scope. Lastly, it should be noted with regard to instant claim 40, although '818 does not specifically claim "phospholipids comprises a gel to liquid crystal transition temperature of greater than 40 degrees Celsius", '818 does claim DPPC in the dependent claims and DPPC has a temperature of 42 degrees Celsius.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 57, 59-80, 82-102 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15, 19-22, 37-49, 52-64, 67-79, 82-83, 94, and 102 of copending Application No. 10/750934. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

The instant application claim 39 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix, with a geometric diameter of 1-30 microns, a bulk density of less than about 0.5 g/cm3,

and an aerodynamic diameter of less than 5 microns. Independent claim 40 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix wherein said phospholipids comprises a gel to liquid crystal transition temperature of greater than 40 degrees Celsius. Dependent claims are directed to active agents selected from antiinflammatories, lung surfactants, antibiotics, antineoplastics, antifungals, specifically insulin, growth factors etc. The phospholipid is selected from dilauroylphosphatidylcholine, dioleylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, dibehenoylphosphatidylcholine, and diarachidoylphosphatidylcholine, and combinations.

‘934 is directed to a pharmaceutical composition comprising particles comprising an active ingredient in a lipid matrix. The particles have a geometric diameter of less than 3 microns and a mass median diameter of less than 20 microns. Dependent claims are directed to a lipid selected from dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, dibehenoylphosphatidylcholine, and diarachidoylphosphatidylcholine. Dependent claims are directed to hollow, porous particles with a bulk density of less than 0.5 g/cm3, 0.3 g/cm3, and 0.2 g/cm3. Dependent claims are directed to the particle further comprising a polyvalent cation and the specification defines the polyvalent cation as calcium, magnesium, and iron. Independent claim is directed to a specific active agent, amphotericin.

Copending application and instant application are different because ‘934’s independent claim is not directed to a metal ion. However, the independent claims have comprising language and the dependent claim is directed to the particle further

comprising polyvalent metal ions. Thus, the combination of a polyvalent ion, phospholipid, and active agent renders a scope that encompasses the scope of the instant application. Thus, both applications are directed to microparticles comprising the critical elements of 1) an active agent, 2) a phospholipid, and 3) a metal ion.

Claims 57, 59-80, 82-102 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-27, 32-39 of copending Application No. 10/982191. Although the conflicting claims are not identical, they are not patentably distinct from each other because:

The instant application claim 39 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix, with a geometric diameter of 1-30 microns, a bulk density of less than about 0.5 g/cm3, and an aerodynamic diameter of less than 5 microns. Independent claim 40 is directed to a powder composition comprising microstructures comprising an active agent, calcium, and a phospholipid in the matrix wherein said phospholipids comprises a gel to liquid crystal transition temperature of greater than 40 degrees Celsius. Dependent claims are directed to active agents selected from antiinflammatories, lung surfactants, antibiotics, antineoplastics, antifungals, specifically insulin, growth factors etc. The phospholipid is selected from dilauroylphosphatidylcholine, dioleylphosphatidylcholine, dipalmitoylphosphatidylcholine, disteroylphosphatidylcholine, dibehenoylphosphatidylcholine, and diarachidoylphosphatidylcholine, and combinations.

‘191 is directed to a pharmaceutical composition comprising active ingredient and a lipid wherein the gel to liquid crystal transition temperature of greater than 57 degrees Celsius. The dependent claims are directed to the lipid components selected from dipalmitoylphosphatidylcholine. Dependent claims further comprise a divalent cation, specifically calcium. Dependent claims are directed to composition in a dry powder form wherein the particles are hollow and porous particles. Dependent claims are directed to the particles having a geometric diameter of less than 20 microns. Dependent claims are directed to the particles with a bulk density of less than 0.5 g/cm3, 0.3 g/cm3, and 0.2 g/cm3.

Copending application and instant application are different since ‘934’s independent claim is not directed to a metal ion. However, the independent claims have comprising language and the dependent claim is directed to the particle further comprising polyvalent metal ions, specifically calcium ions. Thus, the combination of a polyvalent ion, phospholipid, and active agent renders a scope that encompasses the scope of the instant application. Thus, both applications are directed to microparticles comprising the critical elements of 1) an active agent, 2) a phospholipid, and 3) a metal ion.

Response to Arguments

In the request for continued examination filed 4/6/09, applicant did not present any new arguments. As such, the arguments pertaining to the response of 12/5/08 are reiterated below.

Applicant states that the rejections will be addressed upon indication of allowable subject matter. Therefore, the rejections are maintained for the reasons stated above.

Pertinent Prior Art

PGPUB 20020052310 with an effective filing date of 12/29/00 and claiming benefit to US provisional 60/05004 filed 9/15/97 is considered pertinent to applicant's disclosure but does not constitute prior art since the pertinent subject matter regarding divalent cations in section [0093] is not supported in the provisional application of 60/05004. The subject matter claimed in the instant application is supported in US provisional application 60/060337 which has a filing date of 9/29/97.

Conclusion

Claims 57, 59-80, and 82-102 are rejected. No claims are allowed.

All claims are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b).

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to RACHAEL E. WELTER whose telephone number is (571) 270-5237. The examiner can normally be reached 7:30-5:00 Monday-Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sharmila Landau can be reached at 571-272-0614. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

REW

/Lakshmi S Channavajjala/
Primary Examiner, Art Unit 1611
June 21, 2009